

REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the herein remarks and accompanying information, which place the application in condition for allowance.

I.) Status of Claims and Formal Matters

Claims 1-14 were pending in this application. Claims 12-14 have been withdrawn from consideration by the Examiner. Claim 2 has been canceled and incorporated into independent claim 1. Claim 12 has been cancelled. Claims 1 and 11 have been amended. Support for the claim amendments is found both in the originally filed claims and the specification. No new matter has been added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II.) Restriction Requirement is Traversed

Applicants acknowledge that an election of Invention I, claims 1-12, was made with traverse on a telephone conversation held with the Examiner on August 2, 2006.

The Office Action contends that the inventions listed in Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding technical features. In particular, the Examiner alleges that they have different chemical structures which lack a significant corresponding technical feature.

Applicants submit that the restriction is improper. In MPEP 1850, several situations are detailed where a restriction based on unity invention is improper. The most relevant subsection is found under the heading "Intermediate and Final Products." The MPEP states that unity of invention is considered present where the following two conditions are fulfilled:

(A) The intermediate and final products have the same essential structural element, in that:

- (1) The basic chemical structures of the intermediate and final products are the same, or
- (2) The chemical structures of the two products are technically closely interrelated, the intermediate incorporating an essential structural element into the final product; and

(B) The intermediate and the final products are technically interrelated, this meaning that the final product is manufactured directly from the intermediate or is separated from it by a small number of intermediates all containing the same essential structural element.

Clearly, when considering the intermediates of claims 13-14 and the final product of claim 1, these two conditions are fulfilled. Note that on page 12 of the application as originally filed, Applicants state that the four compounds claimed in claim 13 “are key building blocks in the synthesis of compounds according to the present invention.” The synthetic schemes presented later in the specification indicate that these intermediates are important in the production of the final product(s). Thus, the claimed intermediates and the claimed products are technically interrelated.

Consequently, withdrawal of the restriction requirement is earnestly requested.

III.) The Section 112, First Paragraph (Written Description) Rejection is Overcome

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action asserts that the specification fails to teach compounds covering the entire scope of the claimed invention. In particular, the Office Action alleges that in the claimed compounds, the list of possible substituents for the A group on the macrocycle goes beyond what is described in the specification.

To expedite prosecution, claims have been amended to include preferred embodiments. Thus, the limitation from claim 2 has been added to independent claim 1. Support for the claim is found on the final two paragraphs of page 7 of the specification as originally filed.

Consequently, it is requested that the section 112, written description rejection be withdrawn.

IV.) The Section 112, First Paragraph (Enablement) Rejection is Overcome

Claims 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some cancers, does not reasonably provide support for treating all cancers.

Although there is unpredictability in the chemical arts, one of ordinary skill in the art would recognize that a macrocycle that contains the basic epothilone structure would display properties similar to epothilone. The two review articles cited in the specification as originally filed, Nicolaou et al. (*Agnew. Chem. Int. Ed.*) and Flörsheimer et al. (*Expert Opin. Ther. Patents 2001, 95-958*), reveal that the epothilone family of compounds is highly effective against multiple human carcinoma cell lines (see for instance, Table 1 on page 952 of Flörsheimer). As the claimed compounds are structurally analogous to the epothilones, one of ordinary skill in the art would certainly predict that the claimed compounds would also be effective against these various cell lines.

The Office Action also points out that there are no working examples provided in the specification. However, the Examiner is reminded that that working examples are not necessary to satisfy the enablement requirement. For instance, In *In Re Bundy*, 642 F.2d 430, 434, 209 USPQ 48, 51-52 (CCPA 1981), the court ruled that the appellant's disclosure was sufficient to enable one skilled in the art to use the claimed analogs of naturally occurring prostaglandins even though the specification lacked any examples of specific dosages, because the specification taught that the novel prostaglandins had certain pharmacological properties and possessed activity similar to the E--type prostaglandins (MPEP 2164.06(b)). In the present case, one of ordinary skill in the art would consult one of the two recited review articles or the various references cited therein, and would be able to use the claimed compounds in the treatment of various types of cancers.

The Office Actions also rejects claims 11-12 based on the breadth of the claims. Applicants have amended the claims to include the treatment of breast, ovarian, lung and prostate cancer. The Examiner has stated that the specification is only enabling for breast and ovarian cancer. However, the cited literature reveals that the epothilone family of compounds is effective in the treatment of lung and prostate cancer as well. Therefore, a person of ordinary skill would recognize that the claimed analogous compounds are also effective in the treatment of cancer.

Consequently, it is requested that the section 112, enablement rejection be withdrawn.

V.) The Section 112, Second Paragraph Rejection is Overcome

Claims 1-12 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner states that in the claims, the substituents denoted A, U and R² include an infinite number of possible groups.

In response, the claims have been amended to include only select groups for A, U, and R². Consequently, it is requested that the section 112, indefinite rejections be withdrawn.

VI.) The Section 103 Rejection is Overcome

Claims 1-12 were rejected under 35 U.S.C. 103(a) as being obvious over Nicolaou et al. (*Agnew. Chem. Int. Ed.*) in view of Patani et al. (*Chem. Rev.* 1996, 3147-3176). The Office Action asserts that Patani teaches that a carbonyl group can be replaced by SO if the position is not essential to the function of the molecule. Moreover, the Office action alleges that Nicolaou teaches epothilones with a carbonyl rather than a sulfoxide group at the C-5 position of the epothilone ring and that the carbonyl-group is not essential for activity. Thus, the Office Action alleges that there is motivation in the references to replace the C-5 carbonyl group with a sulfoxide group.

It is respectfully pointed out that there is no suggestion in Nicolaou that the C-5 carbonyl of the epothilone ring is expendable. Actually, Nicolaou teaches the direct opposite. On page 2040, column 1, third paragraph, Nicolaou discusses structure activity relationships at region D (refer to Figure 10 on page 2040) of the epothilone ring. Importantly, Nicolaou states that "loss of activity" was observed when the C-5 carbonyl group was reduced and when the C-5 substituent was removed. This statement is contrary to the Examiner's conclusion that "a person of ordinary skill would determine that the position is non-essential to the function of the compound, and may be modified by the advice of Patani et al."

Interestingly, the Examiner's position that the C-5 position is not essential would teach away from making such a substitution. One of ordinary skill in the art would not undertake a difficult multistep synthesis in order to replace a group that was deemed nonessential. Furthermore, even if the Nicolaou reference were interpreted correctly and the C-5 position of

the epothilone ring were considered important, Patani would still teach away from the claimed compounds. Note that on page 3167, in the last paragraph of column 1, Patani states that “sulfoxides and sulfones are recognized as classical bioisosteres suitable for replacement of a carbonyl group.” Thus, Patani implies that there would be no motivation to substitute the carbonyl group with the sulfoxide group to improve the activity of a therapeutically active compound.

In reality, the compounds referenced in Patani (see Figure 67 and Table 39 on page 3167) are far simpler than the epothilone family. In Figure 82, Patani shows a simple ketone moiety where there are no substituents on the positions adjacent to the carbonyl group. In such a simple molecule, there are likely only subtle conformational differences between the carbonyl group and the sulfoxide group.

On the other hand, in the epothilone family, the carbonyl group is embedded in a 16-membered macrocyclic ring. In addition, the positions adjacent to the carbonyl group have a bulky gem-dimethyl group (at C-4) and a methyl group (at C-6). These groups also exert a significant influence on activity (see Nicolaou, page 2040). Moreover, the bulky C-4 and C-6 substituents would be expected to exert a significant influence on the conformation of the C-5 carbonyl carbon atom. Because the sulfur atom is significantly larger and more polarizable than a carbon atom, the influence of the C-4 and C-6 positions would likely be even more pronounced for the sulfoxide than the carbonyl group. Also, such a change in conformation would also influence the extent of hydrogen bonding between the sulfoxide oxygen at the hydroxyl group in the C-3 position. In short, a difference between a sulfoxide group and a carbonyl group would exert a stronger influence on the epothilone type compounds than in the simpler molecules described in Patani.

In advancing the section 112, enablement rejection, the Examiner stated that “the instant claimed invention is highly unpredictable.” However, the Examiner also surmises that out of the plethora of different substitutions that can be envisioned on the epothilone ring, it would be obvious to replace the C-5 carbonyl group with a sulfoxide group. As elaborated above, the motivation for making such a substitution can not be found in Patani, which actually teaches away from the claimed invention. Nicolaou indicates that the C-5 position may be important for activity. However, Nicolaou does not disclose or suggest placing a sulfoxide group at the C-5 position.

Consequently, it is respectfully requested that the section 103 rejection be withdrawn.

VII.) The Provisional Double Patenting Rejection is Overcome

Claims 1-12 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12 and 22 of copending Application No. 10/535,474 in view of Patani et al. (*Chem Rev.* 1996, 3147-3176).

The issue of whether there is indeed double patenting is contingent upon whether the instant claim herewith is indeed considered and, if so, whether the Examiner believes there is overlap with the claim ultimately allowed in the instant application and co-pending Application No. 10/535,474. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to Application No. 10/535,474 will be considered.

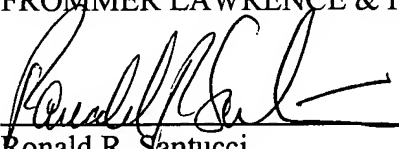
Accordingly, reconsideration and withdrawal of the double patenting rejections, or at least holding them in abeyance until agreement is reached as to allowable subject matter, is respectfully requested.

CONCLUSION

In view of the remarks, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By:


Ronald R. Santucci
Reg. No. 28,988
(212) 588-0800